Arodoxin

Doxorubicin Hydrochloride USP

COMPOSITION

Arodoxin 10 Injection: Each vial contains Doxorubicin Hydrochloride USP 10 mg, as 5 ml concentrated solution for IV Infusion.

Arodoxin 50 Injection: Each vial contains Doxorubicin Hydrochloride USP 50 mg, as 25 ml concentrated solution for IV Infusion.

CLINICAL PHARMACOLOGY

Mechanism of action: Doxorubicin hydrochloride (HCl) is a cytotoxic, anthracycline topoisomerase IIinhibitor. The cytotoxic effect of Doxorubicin HCl on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of Doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of Doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of Doxorubicin HCl cytocidal activity.

Pharmacokinetics: Pharmacokinetic studies conducted in patients with various types of tumors have shown that Doxorubicin follows multiphasic disposition after intravenous injection. The distribution half-life is approximately 5 minutes, while the terminal half-life is 20 to 48 hours. ***Distribution:*** Steady-state distribution volume ranges from 809 to 1214 l/m^2. Binding of Doxorubicin and its major metabolite, Doxorubicinol, to plasma proteins is about 75% and is independent of plasma concentration of Doxorubicin up to 1.1 µg/ml. Doxorubicin does not cross the blood brain barrier. ***Metabolism:*** Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of Doxorubicin HCl. Disposition of Doxorubicinol in patients is formation rate limited, with the terminal half-life of Doxorubicinol being similar to Doxorubicin. The relative exposure of Doxorubicinol, i.e., the ratio between the AUC of Doxorubicinol and the AUC of Doxorubicin is approximately 0.5. ***Excretion:*** Plasma clearance is in the range 324 to 809 ml/min/m^2 and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. In urine, <3% of the dose was recovered as Doxorubicinol over 7 days.

INDICATIONS

Doxorubicin HCl is indicated:

- as a component of multiagent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer.
- for the treatment of acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, metastatic breast cancer, metastatic Wilms' tumor, metastatic neuroblastoma, metastatic soft tissue sarcoma, metastatic bone sarcomas, metastatic ovarian carcinoma, metastatic transitional cell bladder carcinoma, metastatic thyroid carcinoma, metastatic gastric carcinoma, metastatic bronchogenic carcinoma.

DOSAGE AND ADMINISTRATION

Single agent: 60 to 75 mg/m^2 given intravenously every 21 days.

In combination therapy: 40 to 75 mg/m^2 given intravenously every 21 to 28 days.

Doxorubicin HCl should be discontinued in patients who develop signs or symptoms of cardiomyopathy, and dose should be reduced in patients with hepatic impairment.

As an intravenous injection, Doxorubicin HCl is administered through a central intravenous line or a secure and free-flowing peripheral venous line containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP over 3 to 10 minutes. The rate of Doxorubicin HCl administration should be decreased if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. As intravenous Infusion, Doxorubicin HCl is administered only through a central catheter.

Management of Suspected Extravasation: Doxorubicin HCl should be discontinued in case of burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Confirmed or suspected extravasation are managed as follows:

- The needle should not be removed until attempts are made to aspirate extravasated fluid
- The line should not be flushed
- Pressure should not be applied to the site
- Ice should be applied to the site intermittently for 15 min 4 times a day for 3 days
- If the extravasation is in an extremity, extremity should be elevated
- In adults, administration of dexrazoxane should be considered

Incompatibility with Other Drugs: Doxorubicin HCl should not be admixed with other drugs. If Doxorubicin HCl is mixed with heparin or fluorouracil a precipitate may form. Avoid contact with alkaline solutions which can lead to hydrolysis of Doxorubicin HCl.

Dose Modifications:

Cardiac Impairment: Doxorubicin should be discontinued in patients who develop signs or symptoms of cardiomyopathy.

Hepatic Impairment: Doxorubicin HCl is contraindicated in patients with severe hepatic impairment. Decrease the dose of Doxorubicin HCl in patients with elevated serum total bilirubin concentrations as follows:

Serum bilirubin concentration	Doxorubicin HCl Dose reduction
1.2 - 3.0 mg/dl	50 %
3.1 - 5.0 mg/dl	75 %
greater than 5.0 mg/dl	Do not initiate Doxorubicin HCl or Discontinue Doxorubicin HCl

Preparation for Administration:

Reconstitute Doxorubicin hydrochloride injection with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Protect from light following preparation until completion of infusion. All parenteral drug products should be inspected visually prior to administration and should not be used if precipitates, visible particles and/or discoloration is present.

Precautions during Handling: Caution should be exercised in handling Doxorubicin HCl solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing Doxorubicin HCl. If Doxorubicin HCl contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water or sodium bicarbonate solution and flush the mucosa with water.

CONTRAINDICATIONS

Doxorubicin HCl is contraindicated in patients with:

- Severe myocardial insufficiency
- Recent (occurring within the past 4-6 weeks) myocardial infarction
- Severe persistent drug-induced myelosuppression
- Severe hepatic impairment (defined as Child Pugh Class C or serum bilirubin level greater than 5 mg/dl)
- Severe hypersensitivity reaction to Doxorubicin HCl including anaphylaxis

ADVERSE REACTIONS

The most common (>10%) adverse drug reactions are alopecia, nausea and vomiting. Other adverse reactions include- cardiomyopathy and arrhythmias, secondary malignancies, extravasation and tissue necrosis, severe myelosuppression, tumor lysis syndrome, radiation sensitization and radiation recall.

PRECAUTIONS

Pregnancy: Pregnancy Category D. Doxorubicin HCl can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Female patients of reproductive potential should be advised to use highly effective contraception during treatment with Doxorubicin HCl and for 6 months after treatment.

Nursing mothers: There is evidence of Doxorubicinbe excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Doxorubicin HCl, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Pediatric patients treated with Doxorubicin HCl are at risk for developing late cardiovascular dysfunction. Long-term periodic cardiovascular monitoring is recommended for all pediatric patients who have received Doxorubicin HCl.

Geriatric use: No overall differences in safety and effectiveness have been found compared with younger patients.

Hepatic impaired patients: The clearance of Doxorubicin is reduced in patients with elevated serum bilirubin levels. The dose of Doxorubicin HCl should be decreased in patients with serum bilirubin levels greater than 1.2 mg/dl. Doxorubicin HCl is contraindicated in patients with severe hepatic impairment.

DRUG INTERACTIONS

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Avoid concurrent use of Doxorubicin HCl with inhibitors and inducers of CYP3A4, CYP2D6, or P-gp. Concurrent use of Trastuzumab and Doxorubicin HCl results in an increased risk of cardiac dysfunction. Avoid concurrent administration of Doxorubicin and Trastuzumab. Paclitaxel, when given prior to Doxorubicin HCl, increases the plasma-concentrations of Doxorubicin and its metabolites. Administer Doxorubicin HCl prior to Paclitaxel if used concomitantly.

OVERDOSE

The symptoms of overdose are likely to be an extension of Doxorubicin's pharmacological action. Single doses of 250 mg and 500 mg of Doxorubicin have proven to be fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosuppression, the greatest effects of which are seen between 10 and 15 days after administration. Delayed cardiac failure may occur up to six months after the overdose. Patients should be observed carefully and treatment should aim to support the patient during this period.

STORAGE

Store in a dry place at 2°-8° C temperature. Protect from light and do not freeze. Keep out of the reach of children.

PRESENTATION

Arodoxin 10 Injection: Each box contains a single dose glass vial of Doxorubicin HCl 10 mg.

Arodoxin 50 Injection: Each box contains a single dose glass vial of Doxorubicin HCl 50 mg.

Manufactured for:
ARISTOPHARMA LTD.
Shampur•Kadamtali I/A, Dhaka•Bangladesh
by Healthcare Pharmaceuticals Limited, Rajendrapur, Gazipur

20005151/00